AIDS TREATMENT NEWS

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Passive Immunotherapy: Effective Treatment for Advanced AIDS?

by John S. James

In a study described last June at the Stockholm AIDS conference and published last month in The Lancet , researchers treated six persons with advanced AIDS by transfusing blood plasma from donors who were healthy seropositives selected for having a high level of the antibody against the p24 protein of the AIDS virus. The patients had no detectable antibody to p24 before the treatment. But after a single treatment, these patients had the antibody for several weeks--the length of time depending on how much plasma they were given--and showed impressive clinical as well as laboratory improvements. For example, there were ten opportunistic infections among the six patients in the two-month period before treatment, but only one in the two months the treatment was in effect.

This treatment possibility, which is still unproven and not yet in use, is important because it might save lives which could not be saved by any other known means. And technically it would be easy to set up; the only possible obstacle is red tape. Community organizing and support for such an effort may be necessary.

The study is also important because it strongly indicates that persons with even advanced AIDS can recover, if the disease process can be stopped.

Statement of Purpose

AIDS Treatment News reports on experimental and alternative treatments, especially those available now. It collects information from medical journals, and from interviews with scientists, physicians and other health practitioners, and persons with AIDS or ARC.

Long-term AIDS survivors have usually tried many different treatments, and found combinations which work for them. AIDS Treatment News does not recommend particular therapies, but seeks to increase the options available.

We will also examine the ethical and public-policy issues around AIDS treatment research

How the Study Was Done

We will only outline the procedure used because those who need more information can obtain the paper (Jackson and others, 1988--see References).

First the researchers selected two donors who were HIV positive and had very high levels of antibodies to p24 (see "Background" section, below). Then they used plasmapheresis, a routine procedure in blood banks, which separates plasma from cells in the blood, allowing the cells to be returned to the donor. (Plasmapheresis is used in blood banking because donors can replace plasma much more rapidly than cells, allowing more frequent donation, and the plasma itself is often all that is needed for transfusions or for making blood products. Also, plasma usually does not need to be separated by blood type, as whole blood does.)

Then the plasma was frozen and thawed, to rupture any remaining cells, and heat treated to kill any virus. Varying amounts of this treated plasma were infused intravenously into the recipients.

These six patients were severely ill. For example, in the two months before the treatment, five of the six had pneumocystis, and altogether there were ten opportunistic infections. During two months after treatment, there was only one new infection--a fatal case of pneumonia in one patient who had liver disfunction and other complications before the infusion was given, and who did not benefit from the treatment. But after the treatment was discontinued (as part of the experimental design) and after the infused antibodies had disappeared there were nine opportunistic infections among the patients in a two-month period. Other improvements during treatment included weight gain, improved Karnofsky score (a rating of overall health), increased T-helper cells as well as T-8 and T-11 cells, and an immediate disappearance of P24 antigen after infusion of the anti-P24 antibodies. The one test which did not improve was skin sensitivity to antigens.

Before the treatment, viral cultures from the plasma of four of the six patients had been positive. While the treatment was in effect, only one of 36 plasma cultures done was positive. After the treatment period, when the infused antibodies had disappeared, all of nine plasma cultures which were done were positive again. This difference is statistically significant--as was the reduction in opportunistic infections.

Since according to the study design the treatment was not repeated, even if successful, no long-term data was obtained. The treatment proved harmless, however, and there was no indication of viral resistance developing, suggesting that long-term use should be possible.

Background

Previous studies had shown that patients with a high level of antibodies against p24 or p17, which are core proteins of the AIDS virus, usually remained healthy. These and other observations suggested a model of AIDS progression which has become widely known and accepted.

In this model, antibodies to <u>surface</u> proteins of HIV, such as gp120, remain high in patients regardless of whether they do well or not. These antibodies do not tend to neutralize or inhibit the virus.

But antibodies to <u>core</u> proteins of HIV, such as p24, are important indicators. These develop a short time after infection. While they remain high, the person remains a healthy seropositive.

But eventually, for unknown reasons, most patients lose their ability to produce these antibodies, and the level falls to zero, or at least so low that it is undetectable. Then over the next several months, the patient is likely to develop p24 antigenemia, meaning that the p24 viral protein can be detected in the blood. This is what the p24 antigen test measures. (Do not confuse the p24 antigen test, which measures a protein produced by the AIDS virus, with the test for the <u>antibody against</u> the p24 antigen. You want the antigen

to be negative, and the antibody against the antigen to be high. The test for the anti-p24 antibody is not widely available, however.)

Patients with high levels of p24 antigen are more likely to progress to ARC or AIDS during the following months or years. However, some patients with AIDS do not show the p24 antigen.

One study of 57 patients suggested that lack of anti-p24 antibody might be an earlier indicator of risk of progressing to AIDS than the p24 antigen itself, or tests in common use such as T-helper count (Forster and others, 1988). Loss of anti-p24 antibody could precede AIDS by as much as 40 months. We have not yet obtained this paper, only an abstract, so we do not know if any of the 57 patients progressed to AIDS despite having the antibody, or if any remained healthy for a long time without it.

Yet despite the clear fact that lack of anti-p24 antibody was associated with a greater risk of AIDS, it was still not clear that providing this antibody to patients who had lost the ability to make it would be helpful. In fact, during the questioning session after the Stockholm talk by Dr. Jackson, a talk attended by leading AIDS researchers from such institutions as Johns Hopkins, Harvard, and the University of California San Francisco Medical Center, questioners were impressed but also surprised the clinical improvement. Questioners expected the immediate disappearance of p24 after infusion of the antibody--which was observed--but did not expect antiviral activity. In most studies, antibodies to HIV had failed to neutralize (inhibit) it. Dr. Jackson pointed out that some posters being presented at the Stockholm conference had shown that there was at least one site on p24 where an antibody would be neutralizing, although there were other sites where it would not be. In other words, antibody to p24 could have an antiviral effect, although until recently many experts would not have expected it.

Technical Issues

We asked Lisa Bero, Ph.D., a pharmacologist now with the Institute for Health Policy Studies who has several years experience in drug development and has worked extensively with antibodies, to comment on possible technical problems with this treatment. She was concerned that the freezing and heating required to kill the virus might damage the antibodies. While the process seemed to work in the experiment reported, it might not work consistently. Other ways might work better to kill any virus in the plasma. There are standard methods (used in preparing gamma globulin) which can separate antibodies in blood without danger of the product transmitting HIV.

Some tests for the antibody level in the patients treated with the plasma could detect antibodies even if their structure had been damaged by the heat. The particular test (EIA) used by Dr. Jackson's team was a good choice, because it is less likely than others to make this error.

Another possible problem is that patients might develop antibodies against the injected antibodies. This could cause "serum sickness", as well as making injected antibodies ineffective. No sign of such a problem has been observed, however.

Practical Considerations

How long does each treatment with the plasma containing anti-p24 antibodies last? In the study by Dr. Jackson and others, the protective antibodies stayed in the blood from 30 to 70 days, depending on the amount given. With 50 ml of the plasma, antibodies of the recipient would last for about 30 days; with 500 ml, they would last about 70. The data suggested that as little as 5 ml might be effective.

These numbers suggest that one healthy seropositive donor could provide antibodies to maintain at least several people with AIDS, or people at high risk of developing AIDS due to loss of their anti-p24 antibodies.

The treatment did not harm any of the recipients. But precautions were taken, such as observing the patients in the blood bank for one to two hours after the plasma infusion, and then releasing them with an accompanying person.

Would donating protective antibodies be harmful to the donor? It seems unlikely. Six weeks after plasma donation, both donors had antibody levels twice as high as when they donated. In fact, there is substantial evidence that plasmapheresis (the plasma donation) itself can be beneficial to some persons with AIDS, apparently by lowering the level of harmful substances which otherwise accumulate in the blood.

The Next Steps

We do not know of anyone who is using this passive immunotherapy treatment now. Nor could we find anyone by press time who understood how this treatment could fit into the regulatory process and be made available quickly to patients. One activist described what was needed at this time as "breaking the ice"; that is, persons and organizations will have to pioneer and explore options for how the treatment might be made available.

Technically, it would be easy to do. However, private-practice physicians would probably need the cooperation of a blood bank or clinic to do the plasmapheresis and heat treatment of the plasma. They would also need to consult with medical specialists who were up to date on the research. And someone would need to find plasma donors who had high levels of appropriate antibodies.

Two things should be done. We need more research to confirm that the treatment really does work--and to help physicians know how to use it most effectively. Pharmaceutical companies, or community-based research organizations such as the Community Research Initiative, or the U.S. National Institutes of Health, could conduct this research.

But research can go on for years, during which time few people will have access through the trials, so we also need whatever organizing is required to support patients and physicians who want to try passive immunotherapy before all the research is complete. Since plasmapheresis and transfusion of plasma are already standard medical procedures, already regulated to assure good medical practice and patient safety, the same procedures already in use should be available in this case. Physicians clearly have the right to use a standard drug or procedure for a new treatment purpose. Patients who need this treatment, especially those who have no other options, should have access to it without waiting the many years required for approval of new drugs. Results of the treatment should be closely monitored, so that others can benefit from the experience as it becomes available.

Unfortunately the FDA seems unlikely to allow their "treatment IND"--the rules announced over a year ago to make early treatments more available for serious or life-threatening diseases--to be used for passive immunotherapy. (See "Beyond an Unreasonable Doubt: Comments on Drug-Approval Delays", below.) All options will need to be explored.

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